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DOI: https://doi.org/10.1016/j.forsciint.2017.08.007

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Formal publication is available in Forensic Science International, vol. 279, pp 83-87; at https://doi.org/10.1016/j.forsciint.2017.08.007

Abstract

Intoxication cases involving new psychoactive substances (NPS) provide several challenges for forensic toxicologists as data on pharmacodynamic and pharmacokinetic properties are lacking, especially on potency and toxicity. Furthermore, reference values and information on postmortem redistribution (PMR) do not exist so far for most NPS. A fatal case involving the amphetamine-derivatives MDAI (5,6-methylenedioxy-2-aminoindane) and 2-MAPB (1-(benzofuran-2-yl)-*N*-methylpropan-2-amine) was investigated at the Zurich Institute of Forensic Medicine. At admission at the institute approx. 11 h after death (first time point, t1), femoral and heart blood (right ventricle) was collected using computed tomography (CT)-guided biopsy sampling. At autopsy (t2), samples from the same body regions as well as various tissue samples were collected manually. In addition, an antemortem blood sample collected 6 hours before death was available. MDAI and 2-MAPB were quantified using a validated LC-MS/MS method. A significant concentration decrease between the antemortem and the first peripheral postmortem blood sample was observed, which most probably can be explained by remaining metabolism and excretion within the last 6 hours prior to death. No significant concentration change was observed between the two postmortem heart blood and peripheral blood samples. Accordingly, MDAI and 2-MAPB did not seem to undergo relevant postmortem redistribution in peripheral and heart blood in the presented case. This is the first study on postmortem redistribution of the new psychoactive substances MDAI and 2-MAPB. However, more studies covering more cases are necessary to generate universal statements on the PMR with these two NPSs.

Keywords

New psychoactive substances NPS; time-dependent postmortem redistribution; LC-MS/MS; alternative matrices; MDAI, 2-MAPB

Introduction

MDAI (5,6-methylenedioxy-2-aminoindane) and 2-MAPB (1-(benzofuran-2-yl)-*N*-methylpropan-2-amine) belong to the class of new psychoactive substances (NPS). Both analytes are serotonin-releasing agents and appear to have comparable pharmacological effects to MDA and MDMA, but seem to act rather sedative than stimulative [1, 2]. In rodents, MDAI fully substituted for the discriminative-stimulus effects of MDMA [3]. A study in mice investigated the effect of benzofurans and MDMA on the monoamine levels in the mouse corpus striatum. 2-MAPB increased serotonin and dopamine concentrations to the same extent as MDMA, the concentration increase of noradrenaline caused by 2-MAPB, however, was smaller compared to MDMA [2]. To date, only few forensic case reports involving MDAI are available [1]. To the best of our knowledge, no case reports involving 2-MAPB have been published. However, several case reports involving other benzofurans such as 5-APB, 6-APB or 5-MAPB were described [4-8]. In general, NPS are an emerging problem in forensic toxicology with many intoxication cases reported [9]. Such intoxication cases involving NPS provide several challenges for forensic toxicologists as data on pharmacodynamic and pharmacokinetic properties are lacking, especially on potency and toxicity. Furthermore, interpretation of (postmortem) blood concentrations is difficult, as also reference values and information on postmortem redistribution (PMR) of these analytes do not exist so far. PMR complicates interpretation of forensic death cases with drugs involved. Several mechanisms such as e.g. drug degradation, new formation or diffusion processes can contribute to PMR and are believed to be time-dependent [10]. Data on time-dependent PMR is generally rare and mainly exists for classical drugs such as opiates, benzodiazepines, antidepressants or antipsychotics [11-13]. PMR of NPS can only be assumed based on structural similarities to known substances or estimated based on their physicochemical properties such as e.g. lipophilicity or pKa. Structural similarity especially of MDAI to MDMA suggests comparable postmortem behavior to amphetamines. Elliot et al. compared postmortem to antemortem MDMA and MDA concentrations and found the postmortem concentrations to be higher in all cases [14]. Gerostamoulos et al. observed postmortem concentration decreases for amphetamine and methamphetamine; however, they were not significant [11]. The aim of this work was to investigate tissue distribution and time-dependent PMR of MDAI and 2-MAPB in a single authentic case.

Case history

A 27-year old male was found in his bed with a respiratory arrest around 6.50 pm. His wife started resuscitation immediately. The ambulance diagnosed a cardiac arrest and initiated defibrillation including administration of adrenaline, heparin and acetylsalicylic acid with return of spontaneous circulation 40 minutes later. Additionally, flumazenil and naloxone were injected. The pupils were dilated with no reaction to light. Shortly after hospitalization, a second resuscitation was necessary with return of spontaneous circulation 40 minutes later. The blood-gas analysis revealed a severe mixed respiratory-metabolic acidosis with a pH of 6.8, hyperpotassemia of 6.5 mmol/L and hypoglycemia of 2.9 mmol/L. Heart-enzymes, liver enzymes and kidney retention values were elevated. No other striking clinical symptoms were observed including unremarkable computer tomography (CT) of the cranium, thorax and the abdomen. The patient died the next day at 2.47 am (i.e. around 8 h after he had been found in bed). Postmortem autopsy revealed a massive edema of the brain, aspiration pneumonia with lung edema and acutely blood congested internal organs as unspecific intoxication signs. According to his wife he had been an opioid user and had consumed “a handful of” hydromorphone, an

ecstasy derivative and possibly some tramadol two days ago. He had been asleep the whole previous day, unresponsive but always breathing. The night before, he had had nightmares and was snoring.

Material and methods

Chemicals and reagents

An acetonitrilic solution (1 mg/mL) of MDAI was obtained from Sigma-Aldrich Chemie GmbH (Buchs, Switzerland), a methanolic solution (1 mg/mL) of 2-MAPB from Adipogen AG (Liestal, Switzerland) and a methanolic solution (1 mg/mL) of MDMA-d5 from Lipomed AG (Arlesheim, Switzerland). Water was purified with a Purelab Ultra millipore filtration unit (Labtech, Villmergen, Switzerland), acetonitrile of HPLC grade was obtained from Fluka (Buchs, Switzerland) and all other chemicals used were obtained from Merck (Zug, Switzerland).

Antemortem samples

Antemortem samples were collected during hospitalization and delivered to the institute of forensic medicine for further investigation. A urine sample was collected 5.5 hours before death and a blood sample 6 hours before death (t0).

Postmortem samples

Blood and alternative matrices were collected at two time points t1 and t2 after death according to Staeheli et al. [15]. Briefly, after the routine CT imaging procedure (t1, 11 hours after death) on a 128-slice scanner (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany), introducer needles were placed into the right heart ventricle, the right lung, the right lobe of the liver, the spleen, subcutaneous adipose tissue of the waist, muscle tissue at the upper left thigh and the right femoral vein using the virtobot system. After placement of the introducer needles, another CT scan was performed to confirm the needle positions. From the right heart ventricle and the femoral vein, 1 mL blood was collected using a 5 mL syringe. The body fluids were aliquoted in triplicates of 20 µL into 2 mL Eppendorf Safe Lock Tubes (Schoenenbuch, Switzerland). The following day at autopsy (t2, 29 hours after death), samples from the same locations were collected where biopsies had been taken at t1. Additionally, heart blood from the left ventricle, heart muscle tissue from the left ventricle, cerebellum, frontal lobe and gastric content were collected. Urine was not available. After autopsy, the solid matrices were aliquoted into triplicates of approx. 20 mg and body fluids into triplicates of 20 µL. All samples were stored at -20 °C until analysis.

Sample preparation

Extraction of tissue and body fluid samples were performed according to Staeheli et al. [16]. Briefly, organ and tissue samples were homogenized using a Fast Prep®-24 Instrument (MP Biomedicals, Illkirch, France). Two liquid-liquid extractions (LLE) with butyl acetate/ethyl acetate (1:1, v/v) were performed, one at pH 7.4 and one at pH 13.5. The extracts were combined, evaporated to dryness and reconstituted in 60 µL mobile phase.

Routine systematic toxicological analysis

Routine toxicological analysis was performed with blood and urine collected 6 hours before death and with the blood sample collected at autopsy 29 hours after death. Urine was screened initially by a cloned enzyme donor immunoassay (CEDIA®) for drugs of abuse (opiates, cocaine, cannabis, amphetamines, methadone, barbiturates, benzodiazepines, and lysergic acid diethylamide (LSD)), followed by an untargeted LC-MS/MS ion trap screening after simple protein precipitation (Bruker amazon®, Maurer/Wissenbach/Weber database [17]) and for ethanol and other volatile compounds by headspace GC flame ionization detector (HD-GC-FID). Quantification of drugs in peripheral blood was performed by LC-MS/MS.

LC-MS/MS analysis of MDAI and 2-MAPB

The quantitative analysis was performed using a Thermo Fischer Ultimate 3000 UHPLC system (Thermo Fisher, San Jose, California, USA) coupled to a Sciex 5500 QTrap linear ion trap quadrupole mass spectrometer (Sciex, Darmstadt, Germany). The MS was operated in the unscheduled multiple reaction monitoring (MRM) mode using six transitions for MDAI and 2-MAPB each. Three transitions corresponded to the ^{12}C isotope and three transitions corresponded to the ^{13}C isotope of MDAI and 2-MAPB, respectively. Quantifier transitions for MDAI and its ^{13}C isotope were 178→103 and 179→104, respectively. Quantifier transitions for 2-MAPB and its ^{13}C isotope were 190→91 and 191→92, respectively. MDMA-d5 was used as internal standard (IS). Remaining MS settings were according to Staeheli et al. [16]. An LC gradient elution was performed using a Phenomenex (Aschaffenburg, Germany) Synergy Polar RP column (100 x 2.0 mm, 2.5 µm) with 10 mM ammonium formate buffer in water containing 0.1% (v/v) formic acid (pH 3.5, eluent A) and acetonitrile containing 0.1% (v/v) formic acid (eluent B) according to Staeheli et al. [16]. The MS was controlled by Analyst® 1.6.2 software (Sciex) and quantitation was performed with MultiQuant® 2.1.1 software (Sciex). MDAI and 2-MAPB concentrations in urine were calculated using the ^{13}C calibration. Concentrations of all other samples were calculated with the ^{12}C calibration.

Significance of concentration change between t0, t1 and t2 was investigated applying a paired Student`s t-test ($p<0.05$) using GraphPad Prism 6. The concentration ratios between the different matrices and peripheral blood were calculated for t1 and t2.

LC-MS/MS method validation

The method was validated in terms of selectivity, matrix effects, accuracy, precision, calibration model and limits in postmortem femoral blood according to Peters et al. [18].

Selectivity

Six blank postmortem blood samples from different sources and two blank postmortem blood samples spiked with IS (zero samples) were analyzed for interfering peaks with MDAI and 2-MAPB. Selectivity regarding other drugs was investigated injecting a methanolic solution containing a mixture of drugs of abuse, benzodiazepines, antidepressant, neuroleptics and opioids in the concentration of QC high according to Staeheli et al. [16].

Calibration

Eight calibrators were prepared in duplicates at concentrations 5, 25, 100, 200, 500, 1000, 2500, 5000 and 7500 ng/mL. For calibrators 1-5 (1-1000 ng/mL), the ^{12}C isotopes of MDAI and 2-MAPB were used as quantifiers. For calibrators 4-8 (500-7500 ng/mL) the ^{13}C isotopes were used as quantifiers. The regression lines for both calibrations ^{12}C and ^{13}C were calculated using a simple linear model with 1/X weighting. Back calculation of the calibrator concentrations should result in less than ± 20% bias to the theoretical concentration.

Accuracy and precision

Six replicates of quality control (QC) samples at the concentrations levels QC low (7.5 ng/mL), QC med (550 ng/mL) and QC high (6000 ng/mL) were analyzed each on the same day. Concentration of QC low was calculated using ^{12}C calibration (5-1000 ng/mL) and the concentration of QC high was calculated using ^{13}C calibration (500-7500 ng/mL). QC med concentration was determined with both calibrations. Accuracy was calculated as the percent deviation of the mean calculated concentration at each concentration level from the corresponding theoretical concentration. Precision was calculated as the relative standard deviation (RSD) within the QC levels.

Matrix effect and extraction efficiency

Matrix effect and extraction efficiency were investigated with six blank postmortem blood samples from different sources at the concentrations levels of QC med according to Peters et al. [18].

Limits

The limit of quantitation (LOQ) was defined as the concentration of the lowest calibrator (5 ng/mL) fulfilling the criteria of signal to noise 10:1 and back-calculated concentrations within +/- 20% of target. The limit of detection (LOD) was not systematically investigated.

Results and discussion

Routine systematic toxicological analysis

CEDIA® immunoassays in urine were positive for opiates and amphetamines. The LC-ion trap MS screening in urine revealed diphenhydramine. Analysis for detection of NPS in urine was performed at the Institute of Forensic Medicine Freiburg, Germany and identified MDAI and 2-MAPB (Fig. 1). Quantitative analysis in the Zurich Institute of Forensic Medicine (ZIFM) in peripheral blood collected 6 hours before death resulted in 180 µg/L diphenhydramine, and gave negative results for amphetamine, methamphetamine, MDMA, MDEA, opiates and tramadol. Quantitative analysis in peripheral blood collected 29 hours after death revealed 78 µg/L morphine. Due to the lack of morphological findings able to explain death, an intoxication was discussed as the most likely cause of death. However, because of the possibly rather long agonal phase of up to two days, it remained unclear which substances finally contributed to the intoxication. Corkery et al. observed toxic effects of MDAI in the mg/L range [1]. No case reports involving 2-MAPB are available to date. However, for other benzofurans toxic effects were also observed to be in the mg/L range [4, 5]. Therefore, despite the suspected long agonal phase, the concentrations of MDAI and 2-MAPB rather seemed to be too low to be responsible for

death. Next to the amphetamine derivatives and diphenhydramine, other drugs such as opioids might have been involved, which were not detectable anymore at time of hospitalization in blood or urine.

MDAI and 2-MAPB analysis

A short one day method validation was performed for MDAI and 2-MAPB in postmortem blood as proposed by Peters and Drummer for analysis of rarely occurring compounds [18]. No interfering peaks were detected in the blank postmortem blood samples, the zero samples and in the QC high sample containing a mixture of other drugs. For both ^{12}C and ^{13}C calibration a linear regression model with 1/X weighting was used. ^{13}C calibration was used to extend the dynamic range of the method. Concentrations in tissues often exceed blood concentrations to several magnitudes, which demands for a wide dynamic range [15, 19, 20]. Inclusion of the ^{13}C isotope as a quantifier allowed analysis of low and high concentrations using the same sample preparation and analytical method [16, 21]. Validation results including accuracy, precision, matrix effects and extraction efficiency are given in Table 1. Validation exclusively in blood is of course generally not sufficient to evaluate the method performance in other matrices such as postmortem tissues. However, the analytes were included in an already existing method for 83 drugs validated in 11 different postmortem matrices, which was developed to investigate postmortem redistribution of various drugs. In our opinion it is essential to know the distribution of a drug to be able to investigate and interpret its postmortem redistribution. Therefore, the aim was to investigate a large number of matrices. The former validation had shown that accuracy and precision of the applied method was within the required ranges for the majority of the analytes in most matrices as long as an IS had been used [16]. Only 2-MAPB QC med precision exceeded the required limit minimally, which was considered as acceptable due to analysis of triplicate samples in the case investigation. Comparison between time points was performed in a relative manner anyway. Therefore, validation only in postmortem blood was chosen as a compromise between extensive method validation and significance of the expected findings and the resulting accuracy and precision were considered as acceptable.

MDAI and 2-MAPB concentrations at autopsy are displayed in Fig. 2 and Fig. 3, respectively. Both analytes were highest concentrated in gastric content, followed by liver and lung tissue. The high concentrations in gastric content could be explained by oral intake followed by trapping of the basic compounds in the acidic compartment or redistribution into the gastric content. In addition, the gastrointestinal transit might have been inhibited as the person was stated to be an opioid user. High concentrations in liver and lung tissue are often observed for weak bases and could be explained by lysosomal trapping and the high perfusion rate of the organs [22, 23]. Concentrations in heart blood tended to be slightly higher compared to peripheral blood, especially for 2-MAPB. This concentration difference might have been caused by redistribution from the heart muscle by diffusion or from the lung tissue by transport along the pulmonary veins. Lowest concentrations were found in adipose tissue, which was not surprising as the amphetamine derivatives are rather hydrophilic molecules. A urine sample was available only for t0 (antemortem) and contained 1800 µg/L MDAI and 2100 µg/L 2-MAPB. No data on the distribution of MDAI and 2-MAPB within the body was available so far, but found to be comparable to the distribution of MDMA [24, 25].

Time-dependent concentration changes of MDAI and 2-MAPB are displayed in Fig. 4. A significant concentration decrease between the antemortem and the first peripheral postmortem blood sample was observed.

Postmortem redistribution is believed to occur in the first minutes to hours after death [26]. However, the concentration decrease in the presented case can most probably be explained by remaining metabolism and excretion within the last 6 hours before death. Nevertheless, concentration decrease between death and the first postmortem sampling time point t1 cannot be totally excluded, as the concentrations at time of death are unknown. Furthermore, a concentration difference due to comparison of the two different matrices plasma (t0) and whole blood (t1) cannot be excluded. However, blood-to-plasma factors of amphetamines mostly range between 0.7 and 1.3 [24], and are therefore expected to be in the same rather low range for MDAI and 2-MAPB. In addition, stability of the two analytes in postmortem matrices has not been investigated. Therefore, it cannot be excluded that analyte stability contributed to the concentration change between t0 and t1. No significant concentration change was observed between the two postmortem heart blood and peripheral blood samples. In summary, MDAI and 2-MAPB did not seem to undergo relevant postmortem redistribution in peripheral and heart blood in the presented case.

Conclusions

A fatal case involving MDAI and 2-MAPB was investigated for postmortem distribution and redistribution of the two analytes. Distribution of the two analytes was comparable to the distribution of MDMA. No significant postmortem concentration changes for MDAI and 2-MAPB were observed in peripheral and heart blood. Therefore, MDAI and 2-MAPB did not seem to undergo postmortem redistribution in the presented case. However, more studies covering more cases are necessary to generate universal statements on the PMR with these two NPSs.

Artwork and Tables

Table 1 LC-MS/MS method validation results for MDAI and 2-MAPB (matrix effects and extraction efficiencies given with and without IS correction)

Analyte	Isotope calibration	QC	Precision [%]	Bias [%]	Matrix effect +/- RSD [%]	Matrix effect +/- RSD [%] IS corrected	Extraction efficiency +/- RSD [%]	Extraction efficiency +/- RSD [%] IS corrected
2-MAPB	12C	low	-19.6	8.8				
		med	0.0	6.0	84 ± 4	88 ± 6	93 ± 13	112 ± 2
	13C	med	-21.0	8.7	89 ± 5	94 ± 6	87 ± 13	105 ± 3
		high	-1.4	8.4				
MDAI	12C	low	2.2	-5.2				
		med	3.5	-13.3	78 ± 7	81 ± 9	99 ± 5	113 ± 5
	13C	med	9.4	-13.3	80 ± 10	82 ± 15	98 ± 2	109 ± 5
		high	8.7	-6.8				

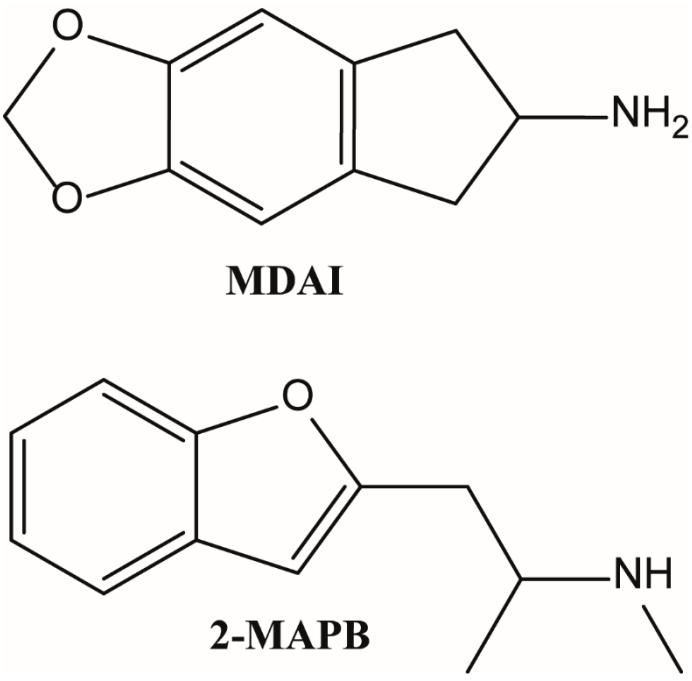

Figure 1 Chemical structures of 2-MAPB and MDAI

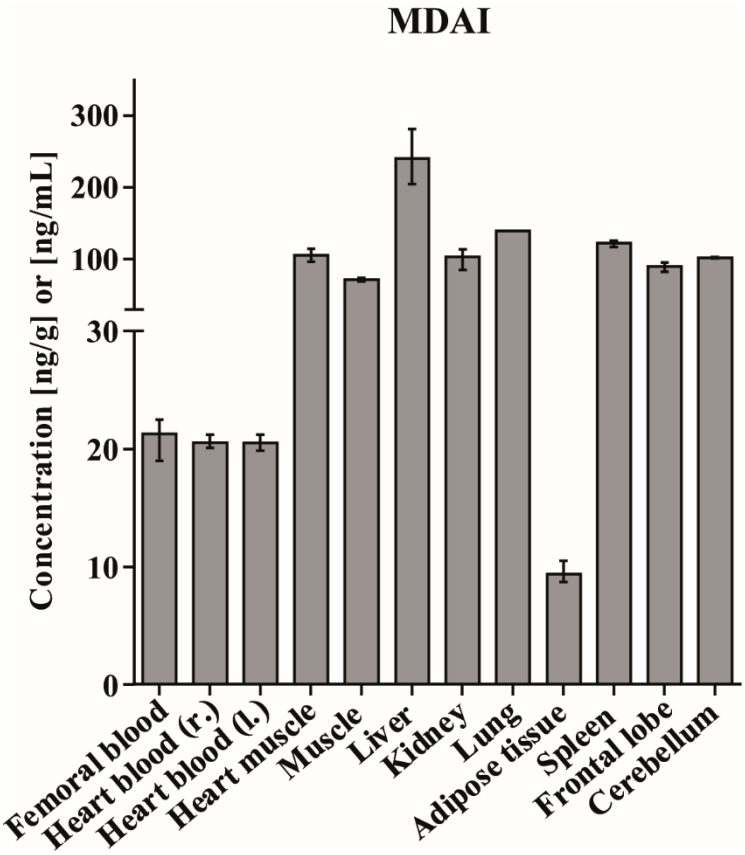

Figure 2 MDAI mean concentrations and ranges of triplicate measurements at autopsy (t2)

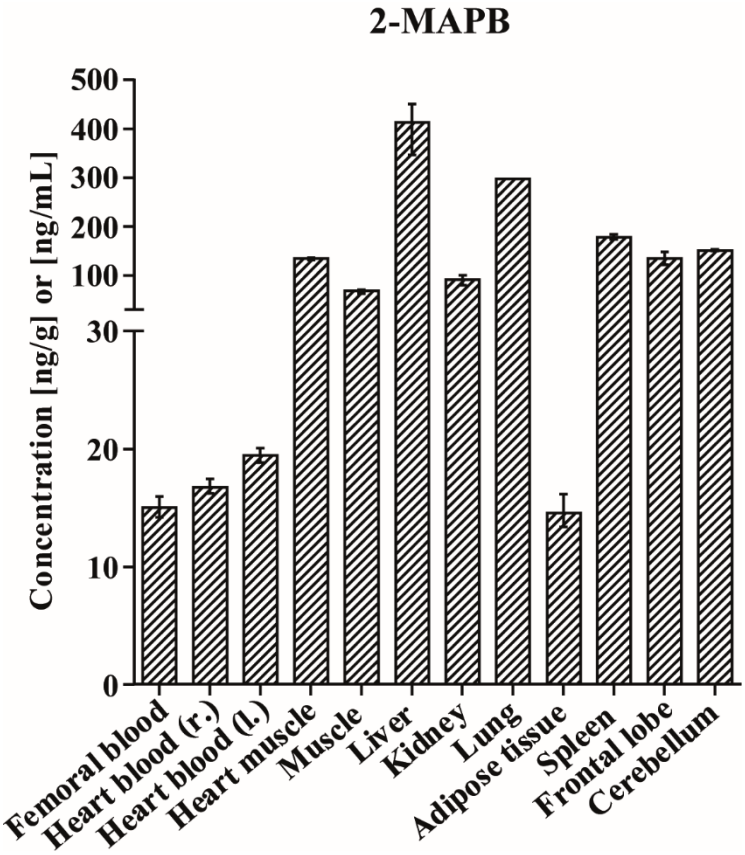

Figure 3 2-MAPB mean concentrations and ranges of triplicate measurements at autopsy (t2)

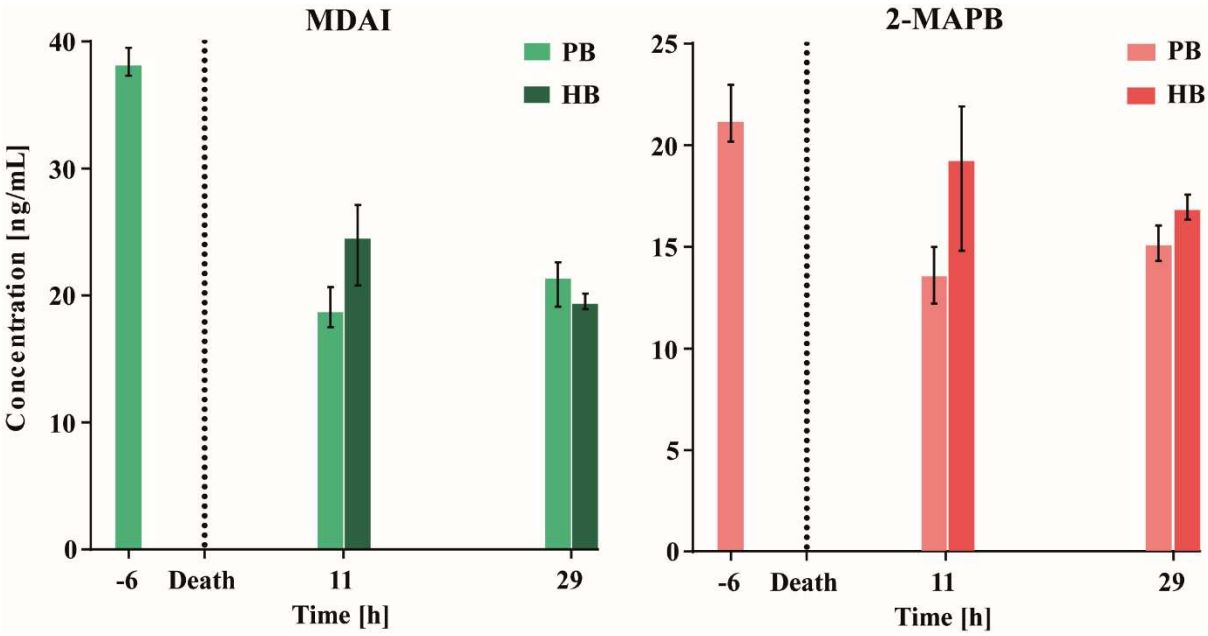

Figure 4 MDAI and 2-MAPB mean concentrations and ranges of triplicate measurements in peripheral blood (PB) collected 6 hours before death at hospital (t0), as well as peripheral blood (PB) and heart blood (HB) collected 11 hours after death using the virtobot system (t1) and 29 hours after death at autopsy (t2)

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